PEPTIC ULCER-A REVIEW ON ETIOLOGY, PATHOGENESIS AND TREATMENT

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ABSTRACT

Peptic ulcers are open sores developing on the inside of the stomach and upper portion of small intestine. A burning stomach is the most common symptom which starts between meals or during nights and it can last for several minutes to hours. It mainly includes gastric and duodenal ulcers. It is caused due to an imbalance between aggressive factors like hydrochloric acid, pepsin, refluxed bile, leukotriene, reactive oxygen species and defensive factors like mucus-bicarbonate barrier, prostaglandins, mucosal blood flow, cell renewal, and migration, non-enzymatic and enzymatic anti-oxidants and growth factors. It is also caused by H. pylori infection, regular use of certain pain relievers like aspirin, ibuprofen but not acetaminophen, Over-The-Counter and NSAID’s. Smoking, alcohol, stress and spicy foods are Certain risk factor of peptic ulcers. Treatment includes the use of certain proton-pump inhibitors, H2 receptor blockers, cytoprotective agents and anti-microbials. This review article includes the etiology, pathogenesis and complete treatment of peptic ulcers.

KEYWORDS: Peptic ulcer, cyclooxygenase enzyme, mitogen activated protein kinases, Prostaglandin.

INTRODUCTION

Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract, mucosa and submucosalis mucosa.\(^1\) It is a break or discontinuity in a bodily membrane that impedes the organ of which that membrane is a part from continuing its proper function. It is a serious disease of the twentieth century. There are different types of ulcers like pressure ulcer (bedsores), genital ulcers, anal fissures, diabetic foot ulcer etc. Among all the above ulcer the most common ulcers are the peptic ulcer, gastric ulcer and the duodenal ulcer. The
former appears to be due to damage to the stomach lining and the latter is characterized by the excessive acid secretion by the oxyntic cells of the stomach. Peptic ulcer develops when the protective mechanisms of the gastric mucosa, bicarbonates and prostaglandins are beleaguered by the detrimental effects of pepsin, gastric acid, Helicobacter pylori and NSAIDs. Various factors that play a pivotal role in development of ulcers are deskbound lifestyle, too much alcohol intake, zesty food, drugs and bacterial contagion. The more serious are the bacterial invasion, NSAIDs and lipid metabolites. NO is considered as a vital GIT mucosal defense mediator. When the concentration of NO is decreased i.e. its synthesis is hampered it contributes to the pathogenesis of ulceration. \(^2\) Treatment includes various types of therapies. These are sequential therapy, quadruple therapy, standard triple therapy and levofloxacin based triple therapy. Chronic use of NSAID in patients with \(H.\text{ pylori}\) infection increases the risk of peptic ulcer disease. That is the reason why patients requiring long term NSAID treatment are recommended for complete eradication of \(H.\text{ pylori}\) before the start of medication.

**ETIOLOGY AND PATHOGENESIS**

The etiology and pathogenesis of peptic ulcers are various \(H.\text{ pylori}\), bacteria, Reserpine, NSAIDs, Gastric Acid secretions, Ethanol, Nitric oxide, Apoptosis, Endothelin etc.

- **\(H.\text{ pylori}\)**

\(H.\text{ pylori}\) is one the major causes of the peptic ulcer disease. It was previously named as \(Campylobacter\text{ pylori}\) is a gram-negative, microaerophilic bacterium found usually in the stomach. It was identified in 1982 by Australian scientists Barry Marshall and Robin Warren. It is linked with development of duodenal and peptic ulcers but 80% of the people infected with the bacteria are asymptomatic and it plays a important role in maintaining proper stomach ecology. Type I strains of \(H.\text{ pylori}\) are pathogenic which encodes the protein cag-A (Cytotoxin-associated gene A). The presence of cag-A gene is probably the best marker of virulence. More powerful release of proinflammatory cytokines with a subsequent potential of mucosal damage is induced by \(H.\text{ pylori}\) bacteria that are cag-A positive. After translocation into host cells it disrupts cell motility, effects cell shape, disrupts cell junction activity and thus responsible for gastric carcinomas and ulcers.\(^3\) It also causes expression of cytokines like TNF-\(\alpha\) in gastritis.\(^4\) \(H.\text{ pylori}\) infected gastric mucosa showed infiltration of polymorphonuclear leucocytes, lymphocytes, monocytes and plasma cells in lamina propria.\(^5\) Acid Hypersecretion occurs when there is pronounced \(H.\text{ pylori}\) induced
inflammation of the antral mucosa in the presence of gastric mucosa. Triple therapy regimens comprising a proton pump inhibitor or ranitidine bismuth citrate and antibiotics like amoxicillin and clarithromycin are standard therapy to treat \textit{H.pylori} infection.\cite{6} Treatment of \textit{H.pylori} induced peptic ulcer disease has improved over the past few decades due to the use of proton pump inhibitors based triple therapy. However the use of NSAIDs and aspirin which has increased over the past few decades are mainly contributing towards this disease.

\begin{itemize}
  \item **NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)**
\end{itemize}

NSAIDS like indomethacin and acetyl salicylic acid is most commonly used as a treatment against arthritis, cardiovascular protection and inflammation. The complication caused due to this usage is the gastric disturbances such as ulcers and erosions.25\% of NSAID users develop gastric complications.\cite{7} The pathophysiology of these complications seems to take place due to their action on COX (cyclooxygenase) inhibition and prostaglandin (PG) deficiency.\cite{8} PGs play a vital role in the mucosal defense system. Any decrease in the COX (cyclooxygenase) leads to a decrease in PG. This is considered as the most important factor of NSAID induced gastric mucosal damage.\cite{9-10} Till date there are two COX forms known.COX-1and COX-2.COX-1 is considered as the” housekeeper” of gastric mucosa i.e. it is responsible for maintaining gastric mucosal integrity whereas COX-2 is responsible for inflammation. Earlier it was considered that, for ulceration to take place COX-1 should be reduced .So, gastric injury was thus considered to the gastric mucosal PG-deficiency by COX-1 inhibition. Recently it was found that not only COX-1 but also COX-2 should be inhibited for ulceration to occur.COX-2 plays the “back up” role of alleviating PG deficiency which is induced by COX-1 inhibition .Inhibition of COX-1 by NSAIDs leads to the release of Endothelin-1 which is a potent vasoconstrictor. This Endothelin-1 is shown to induce gastric injury. This also causes marked decrease in mucosal blood flow. Moreover, gastric acid worsen mucosal injury by deepening lesions and impairing ulcer healing process. Treatment of NSAID induced peptic ulcer involves usage of medications other than conventional histamine 2 receptor blockers and proton pump inhibitors.\cite{11} However if NSAID is discontinued then Histamine 2 receptor blockers and proton pump inhibitors like omeprazole, sucralfate, E-prostaglandin analogs are effective in NSAID induced gastric and duodenal ulcers.\cite{12} Now if NSAID is continued even when GI damage is present then E-prostaglandin analogs like misoprostol, arbaprostil and enprostil are effective in NSAID induced ulcers.\cite{12} Histamine 2 antagonists have especially shown it’s against NSAID induced duodenal ulcers but it is incapable of preventing gastric ulcers.\cite{12} Misoprostol is the only
anti-ulcer drug which is FDA-approved labeling for prevention of NSAID induced gastropathy.\textsuperscript{[11]}

\textbf{Gastric Acid Secretions}

One of the main component of gastric juice is the hydrochloric acid. It is secreted from the parietal or oxyntic cells. Gastric acid is considered as a major ulcerogenic factor in humans and about 50\% of the ulcer patients are acid and pepsin hypersecretors.\textsuperscript{[13]} On the other hand it also plays a protective role by forming the first line of defense of the gastric mucosa against bacterial colonization. \textsuperscript{[14]} Parietal cells bear three stimulators histamine, acetylcholine and gastrin reflecting a triumvirate of neural paracrine and endocrine control. Histamine, secreted from enterochromaffin-like cells may be the primary modulator but the degree of the stimulus appears to be the complex additive or multiplication interactions of each type of signal. Low amounts of histamine only weakly stimulate gastric acid secretions. But if all of the three components are in low proportion then gastric acid secretion rises. There are receptors on the surface of parietal cell which includes Histamine 2 receptor which respond to histamine released from mast cells, receptors that are sensitive to muscarinic effects of acetylcholine and receptors that are sensitive to gastrin. Various studies indicate that there are numerous epithelial cells at the base of pyloric glands which contain histamine and histamine decarboxylase, the enzyme responsible for histamine synthesis. Treatment of Gastric acid secretion induced ulcer includes usage of drugs like Omeprazole, lansoprazole, Rabeprazole, Esomeprazole and Pantoprazole. These drugs are Proton pump inhibitors which block the H+/K+ (ATPase) enzyme system. They are administered along with clarithromycin and amoxicillin (or metronidazole if the patient is allergic to penicillin). Famotidine, Nizatidine and Ranitidine are Histamine 2 receptor blockers. They competitively inhibits Histamine at H2 receptor of the parietal cells of the stomach resulting in decreased gastric acid secretion.

\textbf{Ethanol}

Ethanol also serves as an important ulcer inducing agent in humans and its mechanisms of causing gastric lesions are varied. It includes exhaustion of gastric mucus content with mucosal cell damage. It also includes damaged blood flow to the mucosal cells. The intensive damage to the gastrointestinal mucosa initiates with the microvascular injury. It in turn causes increased vascular permeability, oedema formation and epithelial lifting. Szabo et al suggested that after intragastric administration of ethanol a rapid and time dependent release of endothelin-1 into the systemic circulation preceded the development of hemorrhagic
mucosal erosions by vasoconstrictions.\cite{13} Ethanol is also instrumental behind activating TNF-\(\alpha\) and mitogen activated protein kinases (MAPK).\cite{15} Further, ethanol after metabolism releases superoxide anion and hydroperoxy free radicals which lead to an increased lipid peroxidation.\cite{16}

**DRUGS FOR TREATMENT AND ITS VARIOUS COMPLICATIONS**

There are various medications available for the treatment of peptic ulcer disease. It includes the usage of PPIs (Proton Pump Inhibitors), H2 receptor blockers, Antimicrobials, Cytoprotective agents and Anti-diarrheal agents.

**Proton pump inhibitors**

Drugs under this category works by inhibiting the H+/K+ (ATPase) system, which catalyses the exchange of H+ and K+ ions.

- **Omeprazole**

This drug works by inhibiting the proton pump enzyme system.\cite{17} By this way they reduce the gastric acid secretions from the oxyntic cells of the stomach. They are taken with combination with amoxicillin and clarithromycin (or metronidazole if the patient is allergic to penicillin).\cite{18-19}

**Dosage and strengths (for adults)**

For Packet it is 2.5mg 10mg. As a Suspension it is 2mg/mL. As a Tablet, delayed release it is 20mg. In the form of Capsule, delayed release it is 10mg, 20mg and 40mg.

Duodenal Ulcer-20 mg PO q Day for 4-8 weeks now for the treatment of H.pylori induced peptic ulcers omeprazole is combined with various antibiotics like amoxicillin and clarithromycin. Omeprazole 20mg PO q12hr for 10 days, with Amoxicillin 1000 mg PO q12hr, and Clarithromycin 500 mg PO q12hr for 10-14 days.

**Interactions**

There are various drugs which interact with omeprazole giving antagonistic and synergistic actions. They are as follows:-

**Contraindications**

- Erlotinib- Associated use of erlotinib should be prevented when using PPIs as it reduces its bioavailability and also reduce its solubility.
- Clopidogrel- Omeprazole is an inhibitor of the enzymes CYP2C19 and CYP3A4.\cite{21}
Clopidogrel is an inactive prodrug that partially depends on CYP2C19 for conversion to its active form. Inhibition of CYP2C19 may block the activation of clopidogrel, which could reduce its effects.\(^{[22,23]}\)

Drugs with serious effects when administered with Omeprazole are atazanavir, carbamazepine, ceritinib, cilostazol, clopidogrel, dasatinib, delavirdine and digoxin.

Drugs with minor effects when administered with Omeprazole include alosetron, alprazolam and ambrisentan.

**Adverse Effects**-Omeprazole may cause some adverse effects in our body though in very less amount. These are abdominal pain, diarrhea, nausea, vomiting, flatulence, dizziness, acid regurgitation, constipation and rashes.\(^{[20]}\)

Omeprazole (40mg) is considered to be more effective than omeprazole (20mg) and ranitidine (150mg).\(^{[24]}\)

- **Lansoprazole**
  Like Omeprazole it also decreases gastric acid secretions from the parietal cells by inhibiting the H+/K+ (ATPase) enzyme system. It is administered with amoxicillin and clarithromycin (or metronidazole if the patient is allergic to penicillin).

**Dosage and Strength (for adults)\(^{[26]}\)**
As a capsule/tablet it is 15mg and 30mg and 3 mg/mL in the form of oral suspension.

Duodenal Ulcer: 15 mg PO qDay for 4 weeks
Gastric Ulcer : 30 mg PO qDay for 8 weeks

- **NSAID-associated Gastric Ulcer**
- **Treatment:** 30 mg PO qDay for 8 weeks
- **Prevention:** 15 mg PO qDay for 12 weeks
- **Triple therapy:** Lansoprazole 30 mg + amoxicillin 1 g + clarithromycin 500 mg PO q12hr for 10-14 days
- **Dual therapy (clarithromycin resistant):** Lansoprazole 30 mg + amoxicillin 1 g PO q8hr for 14 days.
- **Penicillin allergy**: Lansoprazole 30 mg + clarithromycin 500 mg + metronidazole 500 mg q12hr for 10-14 days.

**Interactions**[^27]. There are various drugs which interact with lansoprazole giving antagonistic and synergistic actions. They are as follows:

Contraindicated drugs include erlotinib and nelfinavir. Co-administration of lansoprazole with nelfinavir leads to its decreased virologic response and decreased resistance. Mechanism may be CYP2C19 inhibition of Nelfinavir conversion to M8 active metabolite. Serious effects with lansoprazole include atazanavir, dapsone, dasatinib, delavirdine and digoxin. Lansoprazole decreases the effect or level of atazanavir by increasing the gastric pH. Avoid usage of this drug with Lansoprazole or use alternative.

Minor Effects are seen when it affects or decreases the level of lansoprazole by affecting the hepatic enzyme CYP2C19 metabolism the drugs showing minor effects are amobarbital, armodafinil, atazanavir, blessed thistle and bortezomib.

**Adverse Effects**[^28]-Lansoprazole causes the following adverse effects in our body though in very less amount Headache, Diarrhea, Constipation, Nausea, Abdominal pain, Anxiety, Angina and Palpitations are some of the adverse effects.

**H2 Receptor Blockers**

Drugs under this category work by competitively inhibiting Histamine at H2 receptor of gastric parietal cells of the stomach resulting in reduced gastric acid secretions and low concentrations of H+ ion concentration.

**Ranitidine**

It works by competitively inhibiting Histamine at H2 receptor of Gastric parietal cells of the stomach resulting in reduced gastric acid secretions.

**Dosage and Strength (for adults)**[^29]

As an injection solution it is 25mg/mL, 15mg/ml as syrup, as tablet it is 150mg and 300mg.
Interactions\textsuperscript{[30]}

There are various drugs which have a synergistic and antagonistic action with ranitidine. Some of the serious interactions include atazanavir, dasatinib, erlotinib and itraconazole. Minor interactions are alendronate, blessed thistle, ceftibuten and cyanocobalamin.

Adverse Effects\textsuperscript{[31]}-The adverse effects are low with ranitidine. Some of them are headache, abdominal pain, agitation, alopecia, confusion, hallucinations, constipation, diarrhea, thrombocytopenia (rare),\textsuperscript{[32]} pancytopenia (rare) and agranulocytosis (rare).

Anti-microbial

These agents have an antimicrobial action on \textit{H.pylori}. Drugs under this category are Clarithromycin, Metronidazole, Amoxicillin and Tetracycline.

Clarithromycin

It is a semi-synthetic macrolide antibiotic which reversibly binds on the P-site of the 50s ribosomal unit of susceptible organisms and may inhibit RNA protein synthesis by stimulating the dissociation of peptidyl t-RNA from ribosomes thereby causing bacterial growth inhibition.

Dosage and Strengths (for adults)\textsuperscript{[33]}

As oral suspension it is 125mg/5mL and 250mg/5mL, 250mg and 500mg as a tablet.

Peptic Ulcer Disease

500 mg PO q8-12hr for 10-14 days It should be administered as part of 2- or 3-drug combination regimen with bismuth subsalicylate, amoxicillin, H2 receptor antagonist or proton pump inhibitor.

Interactions\textsuperscript{[34]}-Clarithromycin interacts with certain drugs to give synergistic or antagonistic actions. They are as follows

Contraindicated drugs include Astemizole, cisapride, cobimetinib, colchicine, ranolazine, dihydroergotamine and ergotamine. There are many drugs which causes serious effects on the body when taken with clarithromycin. Some of them are afatinib, alitretinoin, almotriptan, alprazolam, amiodarone, amisulpride, amitriptyline, namoxapine, antithrombin alfa and antithrombin. Drugs causing minor effects on the body when taken with clarithromycin are amobarbital, amoxicillin, ampicillin, aprepitant and armodafinil.
**Adverse Effects**[^35]- Adverse effects seen with Clarithromycin are Gastrointestinal (GI) effects, metallic taste (adults), diarrhea, nausea, vomiting, elevated blood urea nitrogen, abdominal pain and rash.

**Cytoprotective agents**
Cytoprotective agents stimulate gastric mucus secretion and also increase blood flow to the gastric mucus. It forms a coating which protects the ulcerated tissue. Examples of cytoprotective agents are misoprostol and sucralfate.

**Misoprostol**
It is a prostaglandin analog which can be used to decrease the incidence of peptic ulcers and NSAID induced ulcers.

**Dosage and strengths[^36]**
As tablet it is used as 100 mcg and 200 mcg.
NSAID induced ulcer

Prophylaxis-200 mcg PO q6hour with food is prescribed but if the dose is not tolerated then it should be reduced to 100 mcg q6hour is given.

**Interactions[^37]**
There are no such drugs which interact with misoprostol causing synergistic or antagonistic actions.

**Adverse Effects**-Some few adverse effects caused by this drug are diarrhea, abdominal pain, headache, anemia cardiac dysrhythmia, chest pain, flatulence, gastrointestinal hemorrhage, hearing loss, myocardial infarction, nausea and rupture of uterus.[^38]

**CONCLUSION**
Peptic ulcers should be detected early as it can lead to serious conditions later. Bleeding ulcers can be a major problem later. Treatments provided above should be followed by the patients accordingly to avoid further spread of the ulcer.

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